OZONATION OF CETIRIZINE, FEXOFENADINE AND HYDROCHLOROTHIAZIDE: DETERMINATION OF RATE CONSTANTS AND NON-TARGET SCREENING FOR THE IDENTIFICATION OF TRANSFORMATION PRODUCTS

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ABSTRACT

The removal of pharmaceuticals by ozonation in water and wastewater is currently widely investigated. However, in the last decades, concern about the formation of transformation products (TPs) has been growing. In the present study, the ozonation of three pharmaceuticals considered as emerging contaminants, cetirizine (antihistamine), fexofenadine (antihistamine), and hydrochlorothiazide (diuretic), were investigated: rate constants were determined followed by the characterization of transformation products. Bench-scale ozonation experiments were conducted with the selected pharmaceuticals (0.1 – 0.4 mM) in ultrapure water, and a competition kinetic method was implemented to determine rate constants k_{O3} for the reaction of the target compounds with ozone. All the selected compounds exhibited a high reactivity with ozone with apparent second order rate constants $k_{O3,app}$ ranging from 10^3 and 10^6 M^{-1} s^{-1} in the pH range 3 – 12. Transformation products formed during ozonation were detected by a non-target approach using LC-HRMS data (Q-Exactive, Thermo Scientific, San Jose, CA) and SIEVE software (Thermo Scientific, San Jose, CA). Depending on the parent compound, this approach revealed between 6 and 16 transformation products, for which a chemical structure was proposed based on the HRMS and HRMS/MS data. When commercially available, transformation products were confirmed with standards and their formation during ozonation was quantified. Formation yields of these transformation products were then calculated and in the case of hydrochlorothiazide reached 85% for the major ozonation products. Based on the TP structures and known reactivity an ozonation pathway was proposed for the three parent compounds. Finally, environmental relevance of the results was studied with real ozonated wastewater or surface water samples. Fast and efficient removal of the selected parent compounds (> 95%) confirmed the potential of ozonation to remove emerging contaminants. Meanwhile, several ozonation products identified during the bench-scale experiments were confirmed to be present in ozonated effluent samples at ng L^{-1} level.

Keywords: Ozonation, pharmaceuticals, Transformation products, High-resolution mass spectrometry, Rate constants

1. Introduction

Ozone is widely used in water and wastewater treatment for disinfection and chemical oxidation of inorganic and organic compounds [1]. Environmental samples are often contaminated by micropollutants like pharmaceuticals and personal care products, pesticides, industrial chemicals. Among them, cetirizine (antihistamine), fexofenadine (antihistamine) and hydrochlorothiazide (diuretic) are commonly detected in Swiss surface waters and wastewaters [2, 3]. Due to their occurrence in environmental samples and the lack of information concerning their fate through wastewater treatment, they are considered as emerging contaminants.

Since their reactivity with ozone has not been investigated yet, the present study aims at (i) describing the ozonation kinetics of these compounds, (ii) identifying the transformation products (TPs) produced during the oxidation of the parent compounds in ultrapure water, and (iii) detecting parent compounds and their TPs in real environmental samples.

2. Material and methods

2.1. Reaction kinetics

Apparent second order rate constants k_{app} were determined in the pH range 2-12 by competition kinetics using cinnamic acid, cresol, benzoquinone or pentenone as competitors. For that, solutions were prepared by dissolving the compound of interest (0.01 mM), the competitor (0.02 mM) and tert-butanol (100 mM) in ultrapure water. The pHs of the solutions ranging from 2 to 12 were adjusted by addition of a phosphate buffer (50 mM). An aliquot (50 µL) of the sample was then analyzed by HPLC-UV.

2.2. Determination of transformation products by suspect and non-target analyses

Solutions (0.4 mM) of pharmaceuticals, called hereafter 'spiked' samples, were prepared in ultrapure water in presence of tert-butanol (100 mM, used as a radical scavenger) and a phosphate buffer (pH 7). In parallel, solutions not spiked with the pharmaceutical were prepared to be used as 'control' samples. All these solutions were subsequently ozonated with different doses of ozone (0.08-4 mM). Without any purification or concentration step the solutions were analyzed by LC-HRMS (Q-Exactive, Thermo Fisher, San Jose, CA). A suspect screening was implemented to detect transformations products predicted by expert knowledge. Subsequently, a non-target analysis was performed to detect other transformation products. Here, a differential profiling of 'spiked' and 'control' samples were automatically carried out using the SIEVE software (Thermo Fisher, San Jose, CA). Detected ions in the ozonated samples were fragmented by targeted HRMS/MS and MS/MS spectra were used for structure elucidation.

3. Results and discussion

The apparent second order rate constant of the compound $k_{app,compound}$ was measured by competition kinetics as described by Hoigné and Bader [4]. Apparent rate constants were determined for each compound and respectively ranged $6 \times 10^3 – 4 \times 10^5$ M^{-1} s^{-1} for cetirizine (over pH range 2 – 11), $4 \times 10^4 – 1 \times 10^6$ M^{-1} s^{-1} for fexofenadine (over pH range 7 – 12) and $2 \times 10^5 – 5 \times 10^5$ M^{-1} s^{-1} for hydrochlorothiazide (over pH range 7 – 12). Since the studied compounds are subject to acid-base dissociation, species-specific rate constants were determined. These results show that ozonation is an efficient process to eliminate these emerging compounds in water and wastewater.

Therefore, it is relevant to elucidate the structure of transformation products, which are formed after ozonation. For that, a suspect screening based on expert knowledge of ozone mechanisms was first implemented. For instance, N-oxides produced during the oxidation of the tertiary amine group [5] were confirmed to be formed after ozonation of cetirizine and fexofenadine. LC-HRMS data from 'Control' and 'Treated' samples were computationally compared to give a list of ions exhibiting significant differences between both groups. Since some ions were likely to be assigned to identical compounds (in-source fragments, adducts, isotopic forms…), a shortlist of significantly different ion was highlighted. Using both suspect and non-target analyses, from 6 to 10 TPs were detected for each parent compounds. Based on further analysis of HRMS and HRMS/MS data, a tentative chemical structure was given to each TP. If commercially available, the proposed chemical structures were confirmed with standards and their formation yields during the treatment were calculated. For instance, in the case of hydrochlorothiazide ozonation, the formation yield of the major TP reached 85%.

While the bench-scale experiments presented above showed the potential of ozonation to remove efficiently the selected parent compounds and to produce a certain number of TPs in ultrapure water, it appeared necessary to evaluate the ozonation process under realistic conditions in a real water matrix. Therefore, samples from a Swiss wastewater treatment plant (ARA Neugut, Dübendorf, Switzerland) using ozonation as an additional treatment were also analyzed by LC-

HRMS/MS. The results from the ozonated effluents confirmed the efficient removal of parent compounds by ozonation as well as the presence of the majority of the previously identified TPs at concentrations above the method detection limit. Additional experiments on the fate of these TPs in biological post-treatments as well as their ecotoxicological activity are planned to be performed in the future.

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